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of FERM BP-5383, FERM P-14879 and FERM P-14880, and wherein said antigen is present on lung adenocarcinoma and not on squamous cell carcinoma, stomach cancer cells, breast cancer cells, and colon cancer cells.

**REMARKS**

Entry of the foregoing and further and favorable consideration of the subject application in light of the following amendments and remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

**I. FORMAL MATTERS**

**A. Finality Withdrawn**

Applicants acknowledge the Examiner's withdrawal of finality and the issuance of a non-final Official Action. See July 7, 2002 Official Action, page 2; Office Action Summary, item 2(b).

**B. Claim Status & Claim Amendments**

As correctly indicated in the Office Action Summary, claims 10-12 and 15 are currently pending in this application.

Claim 10 has been amended to further clarify Applicants' invention. Support for the amendment to claim 10 can be found in the Specification, at least, at page 27, Table 2. Thus, no prohibited new matter has been added by this amendment.

**II. REJECTION UNDER 35 U.S.C. 102(B)**

Claims 10 and 11 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Stein *et al.* HYBRIDOMA 7:555-67 (1988). See July 2, 2002 Official Action, pages 2-3. Applicants respectfully traverse this rejection for at least the following reasons.

Applicants submit that the cited art reference fails to anticipate the claimed invention because the reference fails to disclose each and every element of the claimed invention. It is well established that to anticipate a claim, a single prior art reference must teach, either expressly or inherently, each and every element of the claimed invention, and the single reference must be enabling. See M.P.E.P. § 2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); and Atlas Powder Co. v. E.I du Pont De Nemours & Co., 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). As illustrated below, Stein fails to teach each and every limitation of the claimed invention.

The Examiner has stated that Stein discloses an antigen from the Calu3 human lung adenocarcinoma cell line with a molecular weight of greater than 300 kDa. The Examiner acknowledges that Stein raises antibodies against a membrane preparation of the Calu3 cell line, whereas the antibodies of the instant invention are raised against secreted antigen from the Calu3 cell line. However, the Examiner believes that this difference fails to distinguish the claimed antigen from the one in Stein. In this regard, the Examiner believes that the membrane preparation of Stein contains the claimed

antigen because the antibodies in the instant application, although raised from cell culture medium comprising secreted or shed antigen, are able to bind antigen on the surface of human lung adenocarcinoma same as the antibodies of Stein. The Examiner further argues that the difference in isotype of the antibodies (*i.e.*, IgG for Stein and IgM for the claimed invention) fails to distinguish the claimed antigen from the one in Stein because antibody isotypes do not define the claimed antigen as isotypes define the non-antigen binding effector region of an antibody. Applicants respectfully disagree.

Applicants submit that the specificity of the antibody and antigen disclosed in Stein and the specificity of the antibody that characterizes the antigen of the instant invention differ. In this regard, the antibody in Stein reacts to an antigen that is present on the cell surfaces of lung adenocarcinoma, as well as lung squamous cell carcinoma, stomach cancer, breast cancer, colon cancer, and ovarian cancer. The antibody of Stein even recognizes an antigen present on the cell surface of normal tissue. Thus, the antigen of Stein is present on the cell surfaces of lung adenocarcinoma, lung squamous cell carcinoma, stomach cancer, breast cancer, colon cancer, ovarian cancer, and normal tissue.

By contrast, the antibody corresponding to the claimed antigen only reacts with the specific antigen on lung adenocarcinoma. It does not react with an antigen on the cell surfaces of lung adenocarcinoma, lung squamous cell carcinoma, stomach cancer, breast cancer, colon cancer, ovarian cancer, and normal tissue. Thus, the claimed antigen is not present on the cell surfaces of lung squamous cell carcinoma, lung small cell carcinoma, lung large cell carcinoma, stomach cancer, breast cancer, colon cancer,

and normal tissue. It is only present on lung adenocarcinoma. Accordingly, the antigens of Stein do not characterize a cancer cell of a specific character, but are antigenic substances of the membrane constituents of those cells.

To further illustrate this point, Applicants submit the attached Sheet A which discloses the differences in antibody specificity between the antibody in Stein and the antibody in the instant application. As can be seen, the specificity of the antibody in Stein is clearly different from that of the instant application.

Furthermore, even if the lung cancer cell is focused on, the antigen recognized by the antibody of Stein is present on the cell membrane surfaces of adenocarcinoma and squamous cell carcinoma, while the antigen of the claimed invention is singularly present on the cell surface of adenocarcinoma. It is well established that adenocarcinoma and squamous cell carcinoma are histologically different from each other.

In addition, the difference between the antigen of the instant invention and the antigen of the antibody of Stein is attributable to the different methods of producing the antibodies that recognize those antigens. More specifically, the difference in the immunogen and the screening procedure as shown in attached Sheet B contribute to the antigen difference. In this regard, Stein used only membrane preparations of Calu-3 as an immunogen. In the abstract of Stein, it is stated that "[m]urine monoclonal antibodies (MAbs) reactive with human non-small cell carcinoma of the lung (NSCCL) were produced following immunization with a membrane preparation of Calu-3 . . ." (Emphasis added). Further, on page 557, first paragraph, of Stein, it is stated that

"[a] membrane preparation of Calu-3, a human lung adenocarcinoma cell line grown in nude mice, was used as immunogen." Furthermore, page 560, first full paragraph, of Stein states "[a] panel of tissue culture cell lines and normal human blood cells were tested for reactivity with hybridoma supernatant using an indirect immunofluorescence assay which detects binding of the MAb to cell surface determinants. As shown in Table 1, the antigen was strongly expressed on the immunizing cell line (Calu-3) . . . ." (Emphasis added). This clearly establishes that the monoclonal antibodies raised in Stein were against components in the membrane of the Calu-3 cells.

To the contrary, the antigen/glycoprotein used to raise antibodies in the present invention is a secreted protein. Page 7, last paragraph, of the Specification describes the preparation of the immunogen of the present invention: "An established lung adenocarcinoma cell line, such as Calu-3 (ATCC HTB-55) for example, is cultured in RPMI 1640 medium or MEM medium and then the culture supernatant fluid is recovered. After removing insoluble matter from the thus recovered culture supernatant by centrifugation or using a filter, this is applied to a . . . column to effect adsorption of the antigen in the culture supernatant fluid."

Finally, as previously argued in the Amendment and Reply filed April 2, 2002, the antigen of the claimed invention specifically reacts with an antibody with an IgM isotype. By contrast, the antigen of Stein reacts with an antibody with IgG isotype. Applicants note that the Examiner acknowledges at page 3, lines 25-26, that Stein does not teach an antibody which binds to an antigen from Calu3 cells where said antibody is of the IgM class. See July 2, 2002 Official Action, page 3.

Thus, in view of the above, it is clear that the antigen/glycoprotein of the present invention is a secreted protein found in the supernatant of the cell culture, which is very different from the antigen (*i.e.*, membrane preparation) used by Stein. Clearly, Stein does not disclose the antigen of the instance invention. Therefore, because Stein does not teach each and every element of the claimed invention (*i.e.*, a secreted protein antigen), Stein cannot and indeed does not anticipate the claimed invention.

Furthermore, in order to expedite prosecution in the subject application and not acquiesce to the Examiner's rejection, Applicants have amended claim 10 to recite that the antigen is represented by lung adenocarcinoma and not by squamous cell carcinoma, stomach cells, breast cells, and colon cancer cells. Stein does not teach or disclose this feature. In fact, the specificity of the monoclonal antibody of Stein indicates that the antigen of Stein is present on these other cancer cells.

Therefore, Applicants respectfully request the withdrawal of this rejection.

### III. REJECTIONS UNDER 35 U.S.C. 103(A)

#### A. Stein in view of Wands

Claims 10-12 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Stein *et al.* HYBRIDOMA 7:555-67 (1988) in view of Wands *et al.* US Patent No. 5,422,239. See July 2, 2002 Official Action, pages 3-4. This is a new grounds of rejection.

According to the Examiner, Stein teaches the claimed glycoprotein antigen of claims 10 and 11. The Examiner further indicates that while Stein does not teach an

IgM class antibody which binds to the disclosed antigen from Calu3 cells, it would have been obvious to make such an antibody given the generic teachings in Wands that IgM antibodies have greater sensitivity when compared with IgG antibodies.

Applicants respectfully traverse this rejection for at least the following reasons. Applicants believe that a *prima facie* case of obviousness against the claimed invention has not been made. To establish a *prima facie* case of obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. See M.P.E.P. § 2143.03; In re Royka, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974); In re Zurko, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); In re Wilson, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. See M.P.E.P. § 2143; In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). This element requires that an objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the claimed invention. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In other words, the Examiner must provide a logical reason as disclosed in the prior art at the time of the invention for combining the references along the lines of the invention. Otherwise, the use of such teachings as evidence of non-obviousness will entail impermissible hindsight. Ex parte Stauber, 208 U.S.P.Q. 945, 946 (Bd. App. 1980).

Third, the prior art must provide a reasonable expectation of success. See M.P.E.P. § 2143.02; Vaeck, 947 F.2d at 488, 20 U.S.P.Q.2d at 1438; In re Merck & Co., Inc., 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986).

As to the first required element for establishing a *prima facie* case of obviousness, Applicants submit that the prior art fails to teach the specific monoclonal antibodies that are produced by the specific hybridomas of the claims. In this regard, Applicants reiterate the arguments set forth above with regard to the Stein reference. In particular, and as noted above, Stein fails to teach the specific monoclonal antibodies of claim 10 as evidenced by the differences in binding between these antibodies and the antibodies of Stein. The specificity of the antibody disclosed in Stein and the specificity of the antibody that characterizes the antigen of the instant invention clearly differ. This is clearly evident in that the antibodies in Stein react with antigens present on the cell surfaces of lung squamous cell carcinoma, lung small cell carcinoma, lung large cell carcinoma, stomach cancer, breast cancer, colon cancer, and normal tissue. By contrast, the antibodies of the instant invention do not bind to an antigen present on the cell surfaces of lung squamous cell carcinoma, lung small cell carcinoma, lung large cell carcinoma, stomach cancer, breast cancer, colon cancer, and normal tissue. Instead, they only bind to an antigen present on lung adenocarcinoma.

Furthermore, Wands fails to remedy this deficiency of Stein. Wands also fails to teach the specific monoclonal antibodies of the claimed invention. Instead, Wands is just a general teaching regarding IgM antibodies.

In addition, Stein fails to teach IgM class antibodies. The Examiner allegedly relies on Wands as teaching the desire to generate IgM antibodies. Nonetheless, Wands fails to teach the use of the specific monoclonal antibodies of the claimed invention. Accordingly, the prior art fails to teach or suggest the specific monoclonal antibodies of the claims, and thus they fail to teach each and every element of the claimed invention.

This is especially relevant given that Applicants have amended claim 10 to recite that the antibody recognizes antigen present in lung adenocarcinoma and not in squamous cell carcinoma, stomach cells, breast cells, and colon cancer cells. This amendment was made in order to expedite prosecution in the subject application and not to acquiesce to the Examiner's rejection. Nonetheless, both Stein and Wands fail to teach or suggest this feature. In fact, the monoclonal antibody of Stein clearly recognizes antigens present on these other cancer cells. See Attached Sheet A. Thus, for at least these reasons, Applicants respectfully request the withdrawal of this rejection.

As to the second element, Applicants submit that the prior art references fail to provide the requisite suggestion and/or motivation for one of ordinary skill in the art to combine and/or modify the references to arrive at the claimed invention. In particular, there is no suggestion to produce monoclonal antibodies via the hybridomas selected from the group consisting of FERM BP-3583, FERM P-14879, FERM P-14880.

Likewise, there is no suggestion to utilize antibodies that singularly bind only lung adenocarcinoma and not squamous cell carcinoma, stomach cells, breast cells, and colon cancer cells.

As to the third element, Applicants note that the prior art also fails to provide a reasonable expectation of success at arriving at the claimed invention. As shown in attached Sheet A and as discussed above, the antibodies of the prior art have a wide binding specificity. Accordingly, there is no expectation of binding singularly to only lung adenocarcinoma.

Because the combination of Stein and Wands does not teach or suggest each and every element of the claimed invention and because there is no motivation to combine these references to arrive at the present invention, Applicants submit that the cited reference do not and indeed cannot render the claimed invention obvious. Thus, for the above-stated reasons, Applicants respectfully request the withdrawal of this rejection.

**B. Taniguchi in view of Stein**

Claims 10-12 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Taniguchi EP 232,871 (1987) in view of Stein *et al.* HYBRIDOMA 7:555-67 (1988). See July 2, 2002 Official Action, pages 4-5. This is a new grounds of rejection.

According to the Examiner, Taniguchi teaches a method for diagnosis of human lung adenocarcinoma by contacting a sample with a monoclonal antibody 4G12. This antibody is an IgM class antibody that recognizes an antigen having a molecular weight of 65 kDa. The Examiner indicates that Taniguchi does not teach the specific antigen of claims 10 and 11. The Examiner further indicates that Stein teaches the specific antigens of claims 10 and 11. Thus, the Examiner concludes that it would have been obvious to substitute the antigen of Stein for the antigen of Taniguchi.

Applicants respectfully traverse this rejection for at least the same reasons noted above regarding the Stein and Wands references. In addition, Applicants further submit that Attached Sheet A provides evidence that both Taniguchi and Stein fail to teach the specificity of monoclonal antibodies of the claims. This is further evidence that neither Taniguchi nor Stein teach each and every element of the claimed invention. Thus, because the combination of Taniguchi and Stein does not teach or suggest each and every element of the claimed invention and because there is no motivation to combine these references to arrive at the present invention, Applicants submit that the cited reference do not and indeed cannot render the claimed invention obvious. Accordingly, for the above-stated reasons, Applicants respectfully request the withdrawal of this rejection.

**C. Jost in view of Stein**

Claims 12 and 15 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jost *et al.* U.S. Patent No. 5,888,773 in view of Stein *et al.* HYBRIDOMA 7:555-67 (1988). See July 2, 2002 Official Action, page 5. This is a new grounds of rejection.

According to the Examiner, Jost teaches an immunoassay for a tumor marker using an Fv antibody fragment. The Examiner admits that Jost fails to teach the Fc fragments that bind to the instant antigen. Once again, the Examiner alleges that Stein teaches the specific antigens of the instant invention. Based on these teachings, the

Examiner alleges it would have been obvious to substitute make antibody fragments from antibodies of Stein based on the general teachings of Jost.

Applicants respectfully traverse this rejection for at least the same reasons noted above regarding the Stein, Wands, and Taniguchi references. As noted above, Stein does not teach the same antigens as those of the instant invention. Accordingly, for this reason alone the rejection fails. Furthermore, even assuming *arguendo* that Stein disclosed the same antigen, there is no motivation or teaching in the prior art to take the antibody fragments from the claimed monoclonal antibodies produced via the hybridomas selected from the group consisting of FERM BP-3583, FERM P-14879, FERM P-14880. Likewise, there is no suggestion to utilize antibodies that singularly bind only lung adenocarcinoma and not squamous cell carcinoma, stomach cells, breast cells, and colon cancer cells. Thus, because the combination of Jost and Stein does not teach or suggest each and every element of the claimed invention and because there is no motivation to combine these references to arrive at the present invention, Applicants submit that the cited reference do not and indeed cannot render the claimed invention obvious. Accordingly, for the above-stated reasons, Applicants respectfully request the withdrawal of this rejection.

**D. Jost in view of Stein, and Holtlund**

Claims 10-12 and 15 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jost *et al.* U.S. Patent No. 5,888,773 and Stein *et al.* HYBRIDOMA 7:555-

67 (1988), and further in view of Holtlund *et al.* U.S. Patent No. 5,650,333. See July 2, 2002 Official Action, pages 5-6. This is a new grounds of rejection.

According to the Examiner while neither Stein nor Jost teach Fab fragments, one of ordinary skill in the art would be motivated to make such fragments based on the generic teachings of Holtlund.

Once Applicants respectfully traverse this rejection for at least the same reasons noted above regarding the Stein, Wands, Taniguich, and Jost references. As noted above, Steins does not teach the same antigens as those of the instant invention. Accordingly, for this reason alone the rejection fails. Furthermore, even assuming *arguendo* that Stein disclosed the same antigen, there is no motivation or teaching in the prior art to take the antibody fragments from the claimed monoclonal antibodies produced via the hybridomas selected from the group consisting of FERM BP-3583, FERM P-14879, FERM P-14880. Likewise, there is no suggestion to utilize antibodies that singularly bind only lung adenocarcinoma and not squamous cell carcinoma, stomach cells, breast cells, and colon cancer cells. Thus, Applicants respectfully request the withdrawal of this rejection for essentially the same reasons noted above.

### CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

Application Serial No. 09/350,899

Attorney's Docket No. 032360-009

Page 15

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Jay Williams

Jay F. Williams  
Registration No. 48,036

P.O. Box 1404  
Alexandria, VA 22313-1404  
(703) 836-6620  
*ext 6637*  
Date: December 2, 2002



Application Serial No. 09/350,899  
Attorney's Docket No. 032360-009

**ATTACHMENT - Marked Up Copy of Amended Claim 10 -**

([bracketed] items deleted; underlined items added)

10. (Thrice Amended) A glycoprotein antigen having a molecular weight of 200 kD or more as determined by SDS-PAGE under reducing conditions, which is expressed by cells of human lung adenocarcinoma, and is secreted by said lung adenocarcinoma, wherein said glycoprotein antigen specifically binds to a monoclonal antibody of an IgM isotype produced by a hybridoma selected from the group consisting of FERM BP-5383, FERM P-14879 and FERM P-14880 [, and said monoclonal antibody is an IgM isotype] and wherein said antigen is present on lung adenocarcinoma and not on squamous cell carcinoma, stomach cancer cells, breast cancer cells, and colon cancer cells.

**Application Serial No. 09/350,899**  
**Attorney's Docket No. 032360-009**

**ATTACHMENT - Attached Sheet A**

Sheet A

Comparison of antibody specificities in the application, Stein et al's and Taniguchi et al's.

|                                  | lung cancers   |                         |                      |                      | other cancers  |               |              |
|----------------------------------|----------------|-------------------------|----------------------|----------------------|----------------|---------------|--------------|
|                                  | Adenocarcinoma | squamous cell carcinoma | small cell carcinoma | large cell carcinoma | stomach cancer | breast cancer | colon cancer |
| The application                  | +              | -*                      | -*                   | -*                   | -**            | -**           | -**          |
| Stein et al<br>(Immunohistology) | +              | +                       | ND                   | -                    | ±              | +             | +            |
| Stein et al<br>(Flow cytometry)  | +              | ±                       | ±                    | (ND)                 | ND             | +             | -            |
| Taniguchi et al                  | +              | +                       | -                    | ±                    | +              | +             | -            |

\*Immunohistology, \*\*Enzyme immunoassay

**Application Serial No. 09/350,899**  
**Attorney's Docket No. 032360-009**

**ATTACHMENT - Attached Sheet B**



## Sheet B

### Screening Procedure of Hybrid in the Application

- 1) thereby preparing hybridomas, subsequently selecting a hybridoma capable of producing a monoclonal antibody having low reactivity with a protein recognizable by DF-L1 which is present in normal human serum and having high reactivity with a protein that exists in the culture broth of Calu-3. (P3, OUTLINE OF THE INVENTION, line7-12)

As described above, the hybridoma is selected to produce the antibody having low reactivity with the antigen present in normal human serum and recognized by DF-L1, and having high reactivity with a secreted protein existing in the culture broth of Calu-3 cell.

### Screening Procedure of Hybrid in Stein et al's

- 1) ELISA performed in 96-well polyvinyl chloride plates coated with crude membrane preparation of Calu-3 cells. (P557, Screening Procedure, line2-4)
- 2) screened against a normal liver membrane preparation by ELISA, and against human peripheral white blood cells by Flow cytometry. (P557, Screening Procedure, line6-8)

As described above, selection is made using the binding of Calu-3 cell with a crude membrane as the first index, the non-binding with a normal human liver membrane as the second index, and the non-binding with a human peripheral white blood cells as the third index.

### Reference

#### Screening Procedure of Hybrid in Taniguchi et al's

- e) As disclosed in Detection of the desired antibody-producing hybridoma (P4), hybridoma of which culture supernatant reacts with human lung squamous cancer cell line PC10 is selected. The term "hybridoma" here indicates a fused cell of a lymph cell originating from a human lung squamous cancer patient and mouse melanoma.